Syntheses of Enantiomerically Pure Cyclopent-2-ene-1-carboxylic Acid and (Cyclopent-2-enyl)acetic Acid by Enantioselective Palladium-Catalyzed Allylic Alkylations − Synthesis of Enantiomerically Pure (−)-Chaulmoogric Acid

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Asymmetric Pd-catalyzed allylic alkylations of dimethyl malonate and diethyl 2-acetoxymalonate with 3-chlorocyclopentene, using phosphanyloxazolines **1** and *ent*-**1** as chiral ligands, gave products (–)-**2** and (+)-**3b** with 95 and 99.5% *ee*, respectively. Oxidative degradation of (+)-**3b** furnished (+)-(*R*)-cyclopent-2-ene-1-carboxylic acid [(+)-**4**] with > 99% *ee*. Alkylation product (–)-**2** was transformed into enantiomerically pure (–)-(*R*)-(cyclopent-2-enyl)acetic acid [(–)-**5**] by three simple steps. Availability of (–)-**5** enabled the first synthesis of enantiomerically pure (–)-chaulmoogric acid [(–)-**9**] in three steps.

Introduction

Cyclopent-2-ene-1-carboxylic acid (**4**, aleprolic acid) and (cyclopent-2-enyl)acetic acid (**5**) are simple, but versatile, chiral building blocks that, in enantiomerically pure or enriched form, have served as starting materials for syntheses of numerous natural products and biologically active compounds (Scheme 1). For example, Scheffold et al. prepared (−)-carbovir[1a] from (−)-**4** and the marine natural product (+)-multifidene from (+)-**4**.[1b] Oppolzer et al. used (−)-**4** as starting material for syntheses of (+)-longifolene and (+)-sativene.[1c] (*S*)-(Cyclopent-2-enyl)acetic acid [(+)-**5**] was used by Mislow and Steinberg for a synthesis of (+)-chaulmoogric acid[2a] and by Mangold and Abdel-Moety[2b] for the preparation of (+)-3-(cyclopent-2-enyl)propanoic acid (alepraic acid). These compounds are constituents of chaulmoogra oils, which in addition contain hydnocarpic acid (n = 10), alepric acid (n = 8), aleprylic acid (n = 6), aleprestic acid (n = 4) and aleprolic acid (n = 0). Ikegami et al.[3] developed a synthesis of (+)-hirsutic acid via (1*S*,5*R*,6*S*)-6-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one, which was prepared from (+)-**5** using a procedure of Vandewalle. Corey et al. used (+)- and (−)-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol, obtained from *rac*-**5** by resolution of the enantiomers, as ligands for catalysts in the asymmetric reductions of ketones.[4]

In view of their numerous interesting applications, preparation on a multigram scale of enantiomerically pure **4** and **5** by catalyst-controlled enantioselective syntheses is highly desirable. Here we report on the stereoselective syntheses of enantiomerically pure (*R*)-cyclopent-2-ene-1-carboxylic acid [(+)-**4**] and (*R*)-(cyclopent-2-enyl)acetic acid [(−)-**5**] by using enantioselective palladium-catalyzed alkylations as key steps. Single enantiomers are also readily available by using enantiomeric chiral ligands. We have carried out a synthesis of (−)-chaulmoogric acid as an application of this methodology.

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Results and Discussion

Cyclopent-2-ene-1-carboxylic Acid and (Cyclopent-2-enyl)-acetic Acid

Chapman et al. obtained optically pure (−)-(*S*)- and (+)-(*R*)-**4** from the racemic mixture of the compound by recrystallization of diastereoisomeric salts with (−)- and (+)-α-phenylethylamine, respectively.[5] The yield of this resolution, which required numerous crystallizations, was only 4%. Despite this low yield, no other procedure has since been developed for obtaining optically pure (+)- and (−)-**4**.

Mislow and Steinberg were the first to prepare optically pure (+)-(*S*)-**5**, in ca. 6% yield, using a resolution via their diastereoisomeric salts with brucine.[2a] Ikegami et al. obtained optically pure (+)-**5** by asymmetric hydroboration of methyl (2,4-cyclopentadienyl)acetate and several subsequent steps.[3a] Nishida et al. reported a synthesis of (−)-**5** based on an auxiliary-controlled radical cyclization that furnished the compound with 88% *ee*.[6] Troxler and Scheffold obtained (+)-**5** with 86% *ee* by an ingenious enantioselective cobalamin-catalyzed rearrangement and (−)-**5** with 54% *ee* by Ireland−Claisen rearrangement of (*R*)-(cyclopent-2-enyl)acetate.[7]

Initial attempts to prepare the title compounds by allylic substitution using phosphanyloxazolines of the first genera-

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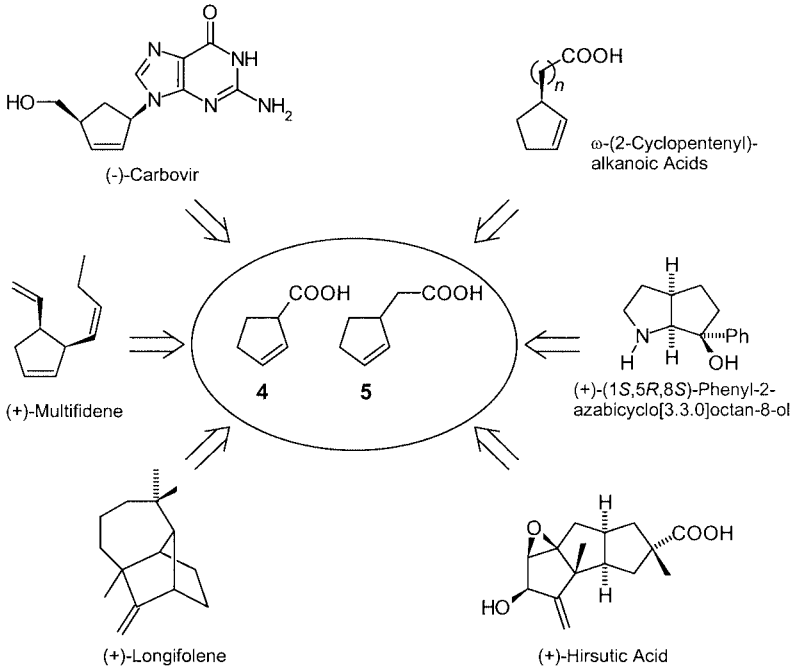
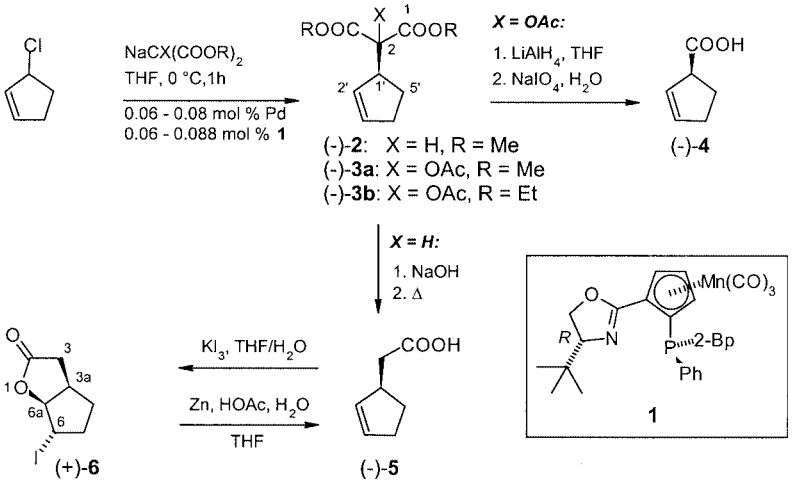


Scheme 1. Applications of carboxylic acids **4** and **5** in natural products synthesis

tion[8] as ligands were frustrated by very low enantiomeric excess (< 20%). With [(phosphanylaryloxazoline)Pd] complexes of the second generation, we prepared (*S*)-(cyclopent-2-enyl)acetic acid with 62% *ee* by allylic alkylation of (cyclopent-2-enyl)acetate with sodium dimethylmalonate.[9a] Excellent results (> 90% *ee*) were obtained with the third-generation ligands **1** and *ent*-**1** (Scheme 2) using (cyclopent-2-enyl)acetate as the substrate.[9b,10] In our earlier work, we used a typical ratio of substrate/catalyst (s/c) of 100:1.

In the next stage of the development, we attempted to increase the s/c ratio by choosing the highly reactive 3-chlorocyclopentene[11] as substrate. Good results were obtained for product (−)-**2** only after considerable experimentation for two reasons: (a) Because of the lack of a procedure for the direct determination of the enantiomeric excess of **2** by chromatography, we had to rely on the determination of the optical purity, based on an optical rotation of $[\alpha]_D^{26} = 98.7$ ($c = 2.27$, $CHCl_3$)[9a] as the reference value; it turned out that this procedure yields values that are consistently too low by ca. 10% (cf. values in Table 1). This feature was established after it was found that enantiomers of the iodolactone **6** could be analyzed by GC on a cyclodextrin phase. Accordingly, for analysis of their enantiomeric excesses, samples of **2** were transformed into iodolactone **6**, by strictly avoiding crystallization, as described in Scheme 2. (b) In small-scale experiments, the enantiomeric excess of



Scheme 2. Asymmetric alkylations and subsequent steps leading to the title compounds. For the sake of brevity, the routes with acetoxymalonates are formulated for the (−)-(*S*) series of products, while those for the (+)-(*R*)-enantiomers were prepared with the help of ligand *ent*-**1**

Table 1. Allylic alkylations of 3-chlorocyclopentene according to Scheme 2

No.	Duration of the Addition of Sodium Dimethylmalonate [min]	Ligand	Product	Yield [%]	Optical purity[a] [%]	*ee* [%]
1	1	**1**	(−)-**2**	75−77	58−64	−
2	20	**1**	(−)-**2**	98	84	92.5[b]
3	60	**1**	(−)-**2**	98	85	95.0[b]
4[c]	120	*ent*-**1**	(+)-**3a**	97	−	98.5
5[c]	120	*ent*-**1**	(+)-**3b**	94	−	99.5

[a] Determined by optical rotation with reference value $[\alpha]_D^{20} = 98.7$ ($c = 2.27$, $CHCl_3$) for the enantiomerically pure compound (ref.[9a]). [b] Determined by GC analysis of iodolactone **6**. [c] Data taken from ref.[13].

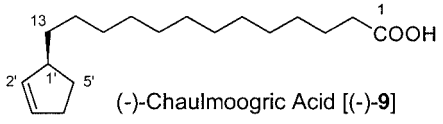
the products from different batches varied considerably. It turned out that the rate of addition of the solution of the nucleophile was a variable of crucial importance (cf. values in Table 1). Excellent results were obtained consistently after complete optimization, even with s/c ratios as small as 1:0.0008 (ratio of Pd/ligand = 1:1 to 1:1.1).

Using the optimal reaction conditions (cf. Scheme 2), the preparative-scale (0.4 mol), Pd-catalyzed asymmetric alkylation with dimethyl malonate gave the alkylation product (−)-**2** in 98% yield with an enantiomeric excess of 92.5%. Saponification of (−)-**2** and decarboxylation of the resulting dicarboxylic acid gave (−)-**5** in 91% yield. Treatment with iodine in a water/THF mixture furnished the iodolactone (+)-**6** with 92.5% *ee*; a single crystallization from ethyl acetate/*n*-pentane sufficed to give the enantiomerically pure (*ee* > 99.5%) compound in 82% yield. Reaction of (+)-**6** with zinc/acetic acid[12] furnished enantiomerically pure (−)-**5** in 82% yield (Scheme 2).

As already reported,[13] the alkylation of sodium dimethyl 2-acetoxymalonate, added over a period of 120 min to the solution of the electrophile, furnished esters **3a** and **3b** with 98.5 and 99.5% *ee*, respectively; the enantiomeric purities were determined by GC on a cyclodextrin phase (entries 4 and 5, Table 1). Ester (+)-**3a** was reduced with lithium aluminum hydride and the resulting crude diol treated with $NaIO_4$ to give cyclopentene-1-carboxylic acid [(+)-**4**] in 92% overall yield.

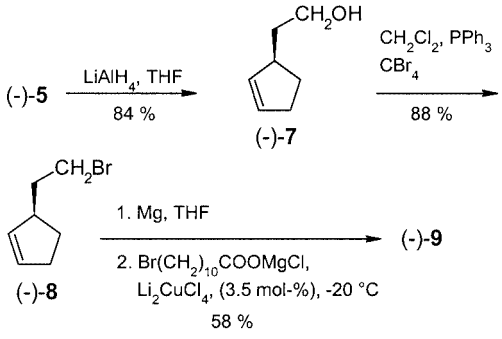
Chaulmoogric Acid

(+)-Chaulmoogric acid [(+)-**9**] was first isolated by Power and Cornall in 1904 from chaulmoogra oil obtained from seeds of *Tarktogenos kurzii*.[14] Chaulmoogra oils have been used in the treatment of leprosy and it was demonstrated that the sodium salt of (+)-**9** displays antibacterial activity against *Mycobacterium leprae*.[2a,15]



The absolute configuration of the natural (+)-chaulmoogric acid [(+)-**9**] was determined by Mislow and Steinberg, who also accomplished the first total synthesis of optically pure (+)-**9** in an overall yield of ca. 2% from chlorocyclopentene.[2a] Wilke and Rink prepared (+)-**9** in 88% yield with 94% *ee* from 3-vinylcyclopentene, which was obtained by asymmetric hydrovinylation of cyclopentadiene in ca. 60% yield.[16] Kaneda demonstrated that (−)-**9** can be obtained with an optical purity of 80% by incorporation of racemic **4** in growing cells of *Bacillus subtilis*.[17]

As (+)-chaulmoogric acid has been prepared several times, we were interested in preparing (−)-chaulmoogric acid from enantiomerically pure (−)-**5** (Scheme 3). Reduction of (−)-**5** with lithium aluminum hydride gave alcohol (−)-**7** (88%) that was transformed into bromide (−)-**8** in 84% yield by reaction with CBr_4/PPh_3.[18] The side chain was completed by copper-catalyzed cross coupling using a procedure developed by Baer and Carney.[19] Thus, 11-bromoundecanoic acid was treated with methyl magnesium chloride to give the corresponding salt that was reacted (catalyst: 3.5 mol % of Li_2CuCl_4)[20] with the Grignard reagent prepared by treatment of (−)-**8** with magnesium (Scheme 3). Pure (−)-chaulmoogric acid [(−)-**9**] was obtained in 58% yield from (−)-**8**; a total yield of 25% from 3-chlorocyclopentene was accomplished. The optical rotation {$[\alpha]_D^{26} = -62.7$ ($c = 4.97$, $CHCl_3$), ref.[2a]: (+)-**9** $[\alpha]_D^{26} = +61.7$ ($c = 4.82$, $CHCl_3$)} and spectroscopic data[21] of (−)-**9** were in excellent agreement with values previously reported.[22]



Scheme 3. Synthesis of (−)-chaulmoogric acid

Conclusion

Enantiomerically pure carboxylic acids (+)- and (−)-**4** as well as (+)- and (−)-**5** are available by Pd-catalyzed asymmetric allylic alkylations of the readily available and cheap 3-chlorocyclopentene, using the phosphanyloxazolines **1** or *ent*-**1** developed in this laboratory as ligands. Acids **4** and **5** can serve as starting materials for the syntheses of numerous natural products; e.g., all of the homologous ω-(cyclopent-2-enyl)alkanoic acids can be accessed in enantiomerically pure form. As an example, (−)-chaulmoogric acid [(−)-**9**] was prepared in 25% overall yield from 3-chlorocyclopentene, using transition metal catalysis in all C−C bond-forming steps.

Experimental Section

General Methods: Melting points and boiling points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 300 spectrometer [300 MHz (^{1}H), 75.46 MHz (^{13}C)] (sh: unstructured signal). Optical rotations were determined with a Perkin−Elmer 241 polarimeter. Polygram Sil G/UV 254 plates (Macherey−Nagel) were used for TLC. The spots were visualized with iodine vapor or by dipping plates into a solution of phosphomolybdic acid in ethanol followed by heating. Fluka silica gel 60 (0.04−0.063 mm) was used for flash chromatography. GLC was carried out on a Hewlett−Packard HP 5890 A instrument equipped with a Chrompack Permethyl β-CD, 50 m × 0.25 mm, column (carrier gas: helium, flow rate: 0.5 mL min^{-1}). GLC/MS was performed on a Hewlett−Packard HP 5890 A gas chromatograph with HP 5972 mass-selective detector using a capillary column HP 1 (crosslinked methyl silicone, 25 m × 0.2 mm, carrier gas: helium).

Dimethyl (−)-(*S*)-(Cyclopent-2-en-1-yl)malonate [(−)-2]: Solution A: Under argon, dimethyl malonate (86.0 g, 0.651 mol) was added dropwise over a period of 20 min to a cooled (0 °C), stirred suspension of NaH (13.4 g, 0.558 mol) in dry THF (1.05 L). The initially grey suspension turned into a clear, colorless solution. Solution B: A solution of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (54.8 mg, 0.15 mmol) and **1** (194.5 mg, 0.33 mmol) in dry THF (50 mL) was cooled to 0 °C, stirred for 10 min under argon, then *freshly distilled* 3-chlorocyclopentene (39.4 g, 0.385 mol) was added dropwise and stirring was continued for 15 min. Solution A was added through a double-ended needle to solution B over a period of 20 min. During the addition, a colorless precipitate was formed. When the addition was complete, the mixture was stirred for 35 min and was then treated with saturated NH_4Cl solution (500 mL). The aqueous phase was extracted with diethyl ether (4 × 400 mL) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo. The resultant red oil (107.5 g) was distilled to give a fraction (56−60 °C/0.01 mbar) of pure (−)-**2** (66.31 g) and a fraction (54−56 °C/0.01 mbar) of impure material, which was purified by flash chromatography [silica (100 g), petroleum ether/ethyl acetate (97:3)] and kugelrohr distillation (95−105 °C/0.01 mbar) to give (−)-**2** (8.19 g; total yield: 98%). [92.5% *ee*, determined via (+)-**6**]. $[\alpha]_D^{20}$ = −82.6 (*c* = 2.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.54 (m, 1 H, 5′-H), 2.08 (m, 1 H, 5′-H), 2.28 (m, 2 H, 4′-H), 3.23 (d, *J* = 9.6 Hz, 1 H, 2-H), 3.32 (m, 1 H, 1′-H), 3.69 (s, 6 H, OCH_3), 5.60 (m, 1 H, 3′-H), 5.79 (m, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.56 (t, CH_2), 31.47 (t, CH_2), 45.18 (d, C-1′), 52.05, 52.06 (2q, OCH_3), 56.45 (d, C-2), 131.11, 132.79 (2d, C-2′, C-3′), 168.84, 168.89 (2s, C=O) ppm. A reaction performed on a 20-mmol scale with the addition of solution A to solution B with a perfusor over a period of 60 min furnished (−)-**2** with 95% *ee*.

(+)-(*R*)-Cyclopent-2-ene-1-carboxylic Acid [(+)-4]: Following our published procedure,[13] (+)-**3a** with 98.5% *ee* was prepared from 3-chlorocyclopentene (97%) using *ent*-**1** as the ligand.

A solution of (+)-**3a** (2.56 g, 10.0 mmol) in THF (150 mL) was added dropwise over a period of 5 min to a cooled (0 °C) suspension of $LiAlH_4$ (1.20 g, 50.0 mmol) in dry THF (20 mL). After stirring at room temperature overnight, workup was carried out by subsequent addition of saturated NH_4Cl solution, acidification to pH 2 with concentrated HCl and complete evaporation of volatiles in vacuo. The solid residue was extracted eight times with portions of ethyl acetate (each 30−50 mL). Extracts were combined and concentrated in vacuo. A solution of the residue (oil) in water (80 mL) was treated with a solution of $NaIO_4$ (6.9 g, 32.5 mmol) in water (50 mL). The mixture was stirred at room temp. for 2 h , acidified to pH 1 with 2 N HCl and extracted with diethyl ether (3 × 150 mL). The organic phase was washed with 2 N HCl and saturated NaCl solution, dried (Na_2SO_4) and concentrated in vacuo. Kugelrohr distillation (5 Torr/90 °C) yielded (+)-**4** as a colorless oil (1.03 g, 92%). $[\alpha]_D^{26}$ = +260.0 (*c* = 1.3, $CHCl_3$), {ref.[5]: $[\alpha]_D^{26}$ = +262.0 (*c* = 3.53, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$): δ = 2.14 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.28−2.53 (sh, 2 H, CH_2), 3.53−3.62 (sh, 1 H, CH-CO), 5.73 (m, 1 H, HC=), 5.91 (m, 1 H, HC=), 11.66 (br. s, 1 H, COOH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.19, 31.98 (2 t, CH_2), 50.20 (d, *C*H-CO), 127.77 (d, HC=), 134.20 (d, HC=), 181.13 (s, COOH) ppm. HR-FAB-MS ($C_6H_8O_2$): calcd. 112.0525; found 112.0529.

(−)-(*R*)-Cyclopent-2-en-1-yl-acetic Acid [(−)-5] with *ee* = 92.5%: An emulsion of (−)-**2** (73.1 g, 0.369 mol, *ee* = 92.5%) in 2.5 N NaOH (370 mL) was heated under reflux for 4 h. The resulting solution was cooled with ice, acidified to pH 1 with concentrated HCl and extracted with diethyl ether (4 × 300 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to give a yellowish solid (64.5 g) that was heated under reflux at 160 °C until evolution of CO_2 ceased (40 min). Distillation (120−125 °C/28 mbar) furnished (−)-**5** as a colorless liquid (42.5 g, 91%). $[\alpha]_D^{20}$ = −87.6 (*c* = 2.00, $CHCl_3$) {ref.[9]: $[\alpha]_D^{20}$ = +109.2 (*c* = 5.9, $CHCl_3$)}.

(+)-(3a*R*,6*S*,6a*S*)-6-Iodohexahydro-2*H*-cyclopenta[*b*]furan-2-one [(+)-6]: A solution of iodine (175 g, 0.69 mol) and KI (340 g, 2.05 mol) in water (800 mL) was added to a mixture of (−)-**5** (42.5 g, 0.34 mol, *ee* = 92.5%), THF (960 mL) and saturated aqueous $NaHCO_3$ solution (640 mL). The resulting mixture was stirred at room temperature for 4.5 h. The mixture was then treated with saturated aqueous $Na_2S_2O_3$ solution until it became colorless and extracted with diethyl ether (4 × 400 mL). The combined organic phases were washed with aqueous 10% $NaHSO_3$ solution (900 mL), water (900 mL) and saturated NaCl solution (900 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting (+)-**6** (81.3 g, 96%, *ee* = 92.5%) was washed with *n*-pentane (50 mL) and dissolved in hot ethyl acetate (20 mL). Addition of *n*-pentane (38 mL) induced crystallization of grey needles (69.9 g) that were isolated and dissolved in diethyl ether (700 mL). For decoloration, the solution was extracted with saturated $Na_2S_2O_3$ solution and the organic layer dried (Na_2SO_4) and concentrated in vacuo to give (+)-**6** (99.9% *ee*) as colorless needles (69.9 g, 82%). M.p. 69−72 °C (ref.[7]: m.p. 68−69 °C). GC: Chrompack Permethyl β-CD, 140 °C, t_R[(−)-**6**] = 29.6 min, t_R[(+)-**6**] = 30.3 min. $[\alpha]_D^{20}$ = +44.1 (*c* =

4.04, CCl_4), {ref.[23]: $[\alpha]_D^{19}$ = +42.5 (*c* = 4, CCl_4)}, $[\alpha]_D^{20}$ = +49.8 (*c* = 0.41, MeOH), {ref.[7]: $[\alpha]_D^{20}$ = +51.8 (*c* = 0.39, MeOH)}. ^{1}H NMR ($CDCl_3$): δ = 1.57 (m, 1 H, 4-H), 1.98−2.19 (sh, 2 H, 5-H), 2.38 (dd, *J* = 18.4, *J* = 2.1 Hz, 1 H, 3-H), 2.40−2.49 (m, 1 H, 4-H), 2.86 (dd, *J* = 18.4, *J* = 10.1 Hz, 1 H, 3-H), 3.09−3.19 (m, 1 H, 3a-H), 4.44 (d, *J* = 4.6 Hz, 1 H, 6-H), 5.17 (d, *J* = 6.1 Hz, 1 H, 6a-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.3 (d, C-6), 32.1 (t, C-4), 34.6 (t, C-5), 35.9 (t, C-3), 36.0 (d, C-3a), 92.3 (d, C-6a), 176.3 (s, C=O) ppm. $C_7H_9IO_2$ (252.05): calcd. C 33.36, H 3.60, I 50.35; found C 33.33, H 3.72, I 50.16.

Enantiomerically Pure (−)-(*R*)-Cyclopent-2-en-1-ylacetic Acid [(−)-5]: A mixture of enantiomerically pure (+)-**6** (6.36 g, 25.2 mmol), THF (44 mL), water (1.4 mL), glacial acetic acid (1.4 mL) and zinc powder (2.86 g, 43.8 mmol) was stirred for 2 h at 0 °C and then filtered through a pad of Celite. The filtrate was concentrated in vacuo and water (200 mL) was added to the residue. The mixture was brought to pH 9 with 1 N NaOH, extracted with dichloromethane (2 × 150 mL), acidified with 1 N HCl to pH 1 and extracted with ethyl acetate (4 × 100 mL). This extract was washed with saturated $Na_2S_2O_3$ solution, dried (Na_2SO_4) and concentrated in vacuo. Kugelrohr distillation (120−130 °C/1.33 mbar) of the residue gave (−)-**5** as a colorless oil (2.57 g, 82%). $[\alpha]_D^{20}$ = −107.8 (*c* = 1.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.47 (m, 1 H, 5′-H), 2.13 (m, 1 H, 5′-H) 2.23−2.46 (sh, 4 H, 4′-H, 2-H), 3.08 (m, 1 H, 1′-H), 5.67 (m, 1 H, 3′-H), 5.77 (m, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.4 (t, CH_2), 31.6 (t, CH_2), 40.0 (t, C-2), 41.5 (d, C-1′), 131.6, 133.2 (2d, C-2′, C-3′), 179.3 (s, C=O) ppm.

(−)-(*R*)-2-(Cyclopent-2-en-1-yl)ethanol [(−)-7]: A solution of enantiomerically pure (−)-**5** (2.54 g, 20.0 mmol) in dry THF (20 mL) was added dropwise over a period of 20 min to a stirred, cooled (0 °C) suspension of $LiAlH_4$ (1.75 g, 50.1 mmol) in dry THF (100 mL). The mixture was heated to reflux for 2.5 h, cooled to 0 °C, and then diethyl ether (200 mL), water (2 mL), 15% NaOH solution (2 mL) and H_2O (6 mL) were added. The mixture was stirred for several hours, filtered and the filtrate dried (Na_2SO_4) and concentrated in vacuo. Kugelrohr distillation (140 °C/35 mbar) of the residue gave (−)-**7** as colorless oil (1.89 g, 84%). $[\alpha]_D^{20}$ = −124.4 (*c* = 2.00, $CHCl_3$), $[\alpha]_D^{26}$= −129.4 (*c* = 2.00, $CHCl_3$), {ref.[2a]: (**+**)-**7**, $[\alpha]_D^{26}$ = +127.4 (*c* = 6.6, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 1 H, 5′-H), 1.48−1.72 (sh, 3 H, 2-H, OH), 2.06 (m, 1 H, 5′-H), 2.29 (m, 2 H, 4′-H), 2.74 (m, 1 H, 1′-H), 3.67 (m, 2 H, C*H*$_2$OH), 5.68 (m, 2 H, 2′-H, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.6 (t, CH_2), 31.7 (t, CH_2), 38.7 (t, C-2), 41.9 (d, C-1′), 61.6 (t, C-1), 130.4, 134.4 (2d, C-2′, C-3′) ppm.

(−)-(*R*)-3-(2-Bromoethyl)cyclopentene [(−)-8]: Tetrabromomethane (9.16 g, 27.6 mmol) was added portionwise over a period of 10 min to a cooled (0 °C) solution of (−)-**7** (2.48 g, 22.1 mmol) and triphenylphosphane (8.72 g, 33.2 mmol) in dry dichloromethane (32.0 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for 12 h, and then it was concentrated in vacuo and the residue stirred for 15 min with diethyl ether (35 mL). The suspension was then filtered and the filtrate concentrated in vacuo. This procedure for removal of triphenylphosphane oxide was repeated three times. Finally, a yellow oil (7.02 g) was obtained that was subjected to kugelrohr distillation (130−140 °C/23 mbar) to furnish (−)-**8** as a colorless oil (3.42 g, 88%). $[\alpha]_D^{20}$ = −67.9 (*c* = 1.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.39 (m, 1 H, 5′-H), 1.82 (m, 1 H, 2-H), 1.94 (m, 1 H, 2-H), 2.06 (m, 1 H, 5′-H), 2.30 (m, 2 H, 4′-H), 2.81 (m, 1 H, 1′-H), 3.40 (m, 2 H, 1-H), 5.64 (m, 1 H, 3′-H), 5.75 (m, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.3 (t, CH_2), 31.9 (t, CH_2), 32.1 (t, C-1), 39.1 (t, C-2), 44.3 (d, C-1′), 131.3, 133.4 (2d, C-2′, C-3′) ppm.

(−)-(*S*)-13-(Cyclopent-2-en-1-yl)tridecanoic Acid [(−)-9] [(−)-Chaulmoogric Acid]: Grignard reagent A: Under argon, a suspension of magnesium turnings (238 mg, 9.80 mmol, activated by dry stirring[24]) in dry THF (2 mL) was treated with a drop of 1,2-dibromoethane. After gentle heating, a solution of (−)-**8** (695 mg, 3.97 mmol) in dry THF (3.5 mL) was added dropwise over a period of 10 min. The mixture was then heated at reflux for 3.5 h. A 1.2-M THF solution (3.50 mL) of methyl magnesium chloride (4.20 mmol) was added dropwise over a period of 1 h to a cooled (−20 °C) solution of 11-bromoundecanoic acid (1.05 g, 3.95 mmol) in dry THF (3.5 mL). After methane evolution was complete, the mixture was stirred at −20 °C for 30 min and then a 0.1-M solution (1.44 mL) of Li_2CuCl_4 (0.14 mmol) in THF and, over a period of 1 h, Grignard reagent A were added dropwise to the cold (−20 °C) mixture. After stirring at −20 °C for 22 h , 2 N H_2SO_4 was added and the resultant mixture was extracted with diethyl ether (4 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a grey solid (1.60 g), which was subjected to flash chromatography [silica gel (550 g), petroleum ether/ethyl acetate/glacial acetic acid, 96:3:1, R_f [(−)-**9**] = 0.11] to give (−)-**9** as a colorless crystal powder (641 mg, 58%). M.p. 68.5−69.5 °C (ref.[2a]: (+)-**9** m.p. 67.7−68.5 °C). $[\alpha]_D^{20}$ = −63.3 (*c* = 4.97, $CHCl_3$), $[\alpha]_D^{26}$ = −62.7 (*c* = 4.97, $CHCl_3$), {ref.[2a]: (+)-**9** $[\alpha]_D^{26}$ = +61.7 (*c* = 4.82, $CHCl_3$)}. ^{1}H NMR (C_6D_6):[25] δ = 1.24−1.63 (sh, 23 H), 2.05−2.16 (m, 1 H, 5′-H), 2.18 (t, *J* = 7.5 Hz, 2 H, 2-H), 2.37 (m, 2 H, 4′-H), 2.74 (m, 1 H, 1′-H), 5.80−5.87 (m, 2 H, 2′-H, 3′-H), 11.3 (br. s, 1 H, COOH) ppm. ^{13}C NMR (C_6D_6): δ = 24.7 (t, C-13), 28.2 (t, CH_2), 29.0 (t, CH_2), 29.4 (t, CH_2), 29.6 (t, CH_2), 29.8 (2t, CH_2), 29.9 (2t, CH_2), 30.0 (t, CH_2), 30.1 (t, CH_2), 32.1 (t, C-5′), 33.9 (t, C-4′), 36.3 (t, C-2), 45.8 (d, C-1′), 130.0, 135.4 (2d, C-2′, C-3′), 180.5 (s, COOH) ppm. GC/MS of the methyl ester of (−)-**9**, obtained by treatment with diazomethane (temperature profile: 50 °C, 3 min, then heating at a rate of 20 °C min^{-1} up to 250 °C): t_R = 14.6 min, *m*/*z* (rel. intensity) = 294 (2) [M^+], 95 (13), 86 (12), 83 (11), 82 (37), 81 (15), 80 (14), 73 (16), 67 (100), 66 (11), 55 (17). $C_{18}H_{32}O_2$ (280.44): calcd. C 77.09, H 11.50; found C 77.05, H 11.37.

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[1] [1a] S. Hildbrand, T. Troxler, R. Scheffold, *Helv. Chim. Acta* **1994**, *77*, 1236−1240. [1b] S. Hemamalini, R. Scheffold, *Helv. Chim. Acta* **1995**, *78*, 447−451. [1c] W. Oppolzer, T. Godel, *Helv. Chim. Acta* **1984**, *67*, 1154−1167.
[2] [2a] K. Mislow, I. V. Steinberg, *J. Am. Chem. Soc.* **1955**, *77*, 3807−3810. [2b] E.M. Abdel-Moety, H. K. Mangold, *Chem. Phys. Lipids* **1980**, *26*, 279−283.
[3] [3a] M. Nishida, K. Iseki, M. Shibasaki, S. Ikegami, *Chem. Pharm. Bull.* **1990**, *38*, 3230−3237. [3b] P. Callant, H. De Wilde, M. Vandewalle, *Tetrahedron* **1981**, *37*, 2079−2084.
[4] E. J. Corey, C. P. Chen, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5547−5550.
[5] O. L. Chapman, K. C. Mattes, R. S. Sheridan, J. A. Klun, *J. Am. Chem. Soc.* **1978**, *100*, 4878−4884.
[6] M. Nishida, H. Hayashi, Y. Yamaura, E. Yanaginuma, O. Yonemitsu, A. Nishida, N. Kawahara, *Tetrahedron Lett.* **1995**, *36*, 269−272.
[7] T. Troxler, R. Scheffold, *Helv. Chim. Acta* **1994**, *77*, 1193−1202.

[8] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769−1772.
[9] [9a] P. Sennhenn, B. Gabler, G. Helmchen, *Tetrahedron Lett.* **1994**, *35*, 8595−8598. [9b] S. Kudis, G. Helmchen, *Angew. Chem.* **1998**, *110*, 3210−3212; *Angew. Chem. Int. Ed.* **1998**, *37*, 3047−3050.
[10] [10a] G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336−345. [10b] G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.* **1996**, *96*, 513−518.
[11] R. B. Moffet, *Org. Syntheses*, Coll. vol. IV, **1963**, 238−241.
[12] J. C. Florent, J. Ughetto-Monfrin, C. Monneret, *J. Org. Chem.* **1987**, *52*, 1051−1056.
[13] S. Kudis, G. Helmchen, *Tetrahedron* **1998**, *54*, 10449−10456.
[14] F. B. Power, F. H. Cornall, *J. Chem. Soc.* **1904**, *85*, 839−861.
[15] [15a] G. S. Hiers, R. Adams, *J. Am. Chem. Soc.* **1926**, *48*, 1089−1093. [15b] L. Levy, *Am. Rev. Respir. Dis.* **1975**, *111*, 703−705. [15c] M. Hooper, *Chem. Soc. Rev.* **1987**, *16*, 437−465.
[16] [16a] G. Wilke, in *Organometallics in Organic Synthesis 2*, (Eds.: H. Werner, G. Erker), Springer, Heidelberg, **1989**, p. 1. [16b] S. Rink, *Dissertation*, Universität Bochum, **1989**.
[17] T. Kaneda, *Biochem. Biophys. Res. Commun.* **1981**, *99*, 1226−1229.
[18] P. J. Kocienski, G. Cernigliaro, G. Feldstein, *J. Org. Chem.* **1977**, *42*, 353−355.
[19] T. A. Baer, R. L. Carney, *Tetrahedron Lett.* **1976**, *51*, 4697−4700.
[20] M. Tamura, J. Kochi, *Synthesis* **1971**, 303−305.
[21] P. Blaise, M. Farines, J. Soulier, *J. Am. Oil Chem. Soc.* **1997**, *74*, 727−730.
[22] After completing the present investigation, we prepared enantiomerically pure iodolactone (−)-**6** in conjunction with the syntheses of archaea lipids. Using this compound, we transformed it, using the route described above, into (+)-chaulmoogric acid, $[\alpha]_{26}^{D} = +62.4$ ($c = 5.0$, $CHCl_3$), in 40% overall yield.
[23] R. K. Hill, A. G. Edwards, *Tetrahedron* **1965**, *21*, 1501−1507.
[24] J. M. Brown, K. V. Baker, N. Hughs, A. J. Skarnulis, A. Sexton, *J. Org. Chem.* **1991**, *56*, 698−703.
[25] All signals were assigned on the basis of H,H-COSY and C,H-COSY experiments.

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